

The Identification of Marker's ' α -Ketodihydrolanosteryl Acetate ' as 3 β -Acetoxy lanost-9(11)-en-7-one

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In addition to 3 β -acetoxy lanost-8-en-7-one (5) and 3 β -acetoxy lanost-8-ene-7,11-dione (6), known products of the reaction, oxidation of 3 β -acetoxy lanost-8-ene (1) with chromic acid-acetic acid at 80° afforded 3 β -acetoxy lanost-9(11)-en-7-one (4), apparently identical with Marker's ' α -ketodihydrolanosteryl acetate '. Oxidation of 3 β -acetoxy-8 α ,9 α -epoxy lanostane (2) and 3 β -acetoxy lanost-7,9(11)-diene (3) under the same conditions yielded the same three products.

IN 1937, before the structure of lanosterol was established, Marker and his co-workers¹ oxidised 3 β -acetoxy lanost-8-ene (1) with chromic acid-acetic acid at 80° for 10 min and obtained ' α -ketodihydrolanosteryl acetate,' C₃₂H₅₂O₃, m.p. 150°, and ' β -ketodihydrolanosteryl acetate,' m.p. 152°. The β -isomer was later identified by Barton and his co-workers² as 3 β -acetoxy lanost-8-en-7-one (5). Repetition of the oxidation by later workers, however, has failed to yield the α -isomer.

Oxidation of compound (1) under Marker's conditions has now given three products, separated by column chromatography on deactivated alumina. One was identified as the conjugated enone (5), the second as the diketone (6), and the third, C₃₂H₅₂O₃, m.p. 150—152°,

isomeric with the enone (5) is, in all probability, Marker's ' α -ketodihydrolanosteryl acetate,' with structure (4).

The compound does not absorb strongly in the u.v. above 220 nm, but i.r. bands at 1730 and 1700 cm⁻¹ indicate the presence of acetate and saturated carbonyl groups, respectively. The n.m.r. spectrum exhibits a one-proton vinyl resonance at δ 5.43 and a one-proton singlet at δ 2.32, values consistent with the presence of a 9,11-double bond. A weak negative Cotton effect, similar to that of β -acetoxy lanostan-7-one (7), indicates β -stereochemistry for the 8-proton. These facts support the identification as 3 β -acetoxy lanost-9(11)-en-7-one (4).

Marker's ' α -ketodihydrolanosteryl acetate ' had a melting point (150°) similar to that of compound (4)

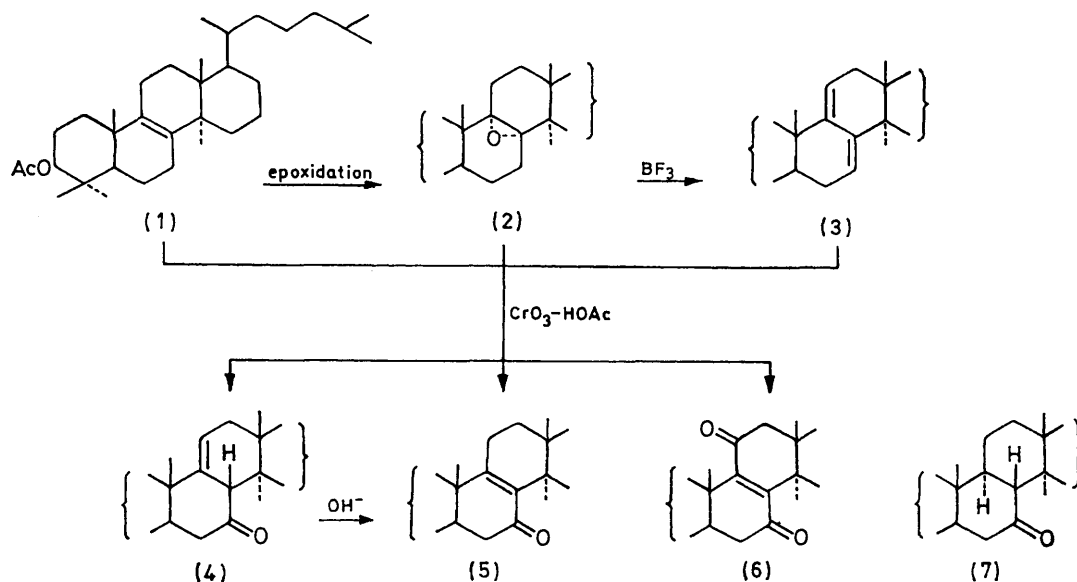
¹ R. E. Marker, E. L. Wittle, and L. W. Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368.

² D. H. R. Barton, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 1951, 3147.

and underwent alkaline hydrolysis to 'β-ketodihydro- lanosterol' (3β-hydroxylanost-8-en-7-one²) (5; OH for OAc), whose constitution was proved by acetylation to 3β-acetoxylanost-8-en-7-one (5). Since alkaline hydrolysis of the acetate (5) also afforded the same hydroxy- compound (5; OH for OAc), a simple isomerism of an unconjugated to a conjugated enone must have occurred during the first hydrolysis. Our own product (4) was also isomerised to the conjugated enone (5; OH for OAc) by alkali. Although a direct comparison has not been made, the foregoing evidence indicates that Marker's

A solution of 3β-acetoxylanost-3-ene (2.0 g, 42 mmol) in acetic acid (60 ml) at 80° was added rapidly to a solution of chromium trioxide (1.08 g, 10.8 mmol) in acetic acid (90%; 40 ml) and the mixture was maintained at 80° for 10 min. The cooled solution was poured into water (250 ml) and the precipitate was extracted with ether and worked up to yield a solid (2.1 g). This was chromatographed on deactivated alumina (120 g).

(i) Elution with light petroleum-benzene (4 : 1; 400 ml) gave a solid (0.35 g) which crystallised from chloroform-methanol as silky needles of 3β-acetoxylanost-9(11)-en-7-one (4) (0.3 g, 15%), m.p. 150–152°, $[\alpha]_D^{25} +78^\circ$ (c 0.86), o.r.d.



'α-isomer' has the structure (4). Barton and his co-workers³ also obtained compound (4), but only as a mixture with the enone (5). It was also transformed as above into the enone (5).³

3β-Acetoxy-8α,9α-epoxylanostane (2)⁴ and 3β-acetoxylanosta-7,9(11)-diene (3)⁴ are both oxidised under Marker's conditions to the same products [(4)–(6)].

EXPERIMENTAL

U.v. spectra were determined for solutions in ethanol with a Unicam SP 800A or Perkin-Elmer 137 spectrophotometer, i.r. spectra for solutions in chloroform with a Perkin-Elmer 237 spectrophotometer, n.m.r. spectra for solutions in deuteriochloroform with a Varian A60 spectrometer, with tetramethylsilane as internal reference, and optical rotations for solutions in chloroform with a Jasco ORD-UV 5 spectrometer.

Oxidation of 3β-Acetoxy-8-ene under Marker's Conditions.—3β-Acetoxy-8-ene, obtained as a by-product in the purification of lanosterol from 'isocholesterol' (purchased from van Schnappen and Soon, Veenendaal, Holland) by Bloch's method,⁵ had δ 0.68 (3H, s, 18-H₃), 1.00 (3H, s, 19-H₃), 2.98 (3H, s, 3-OAc), and 4.42 (1H, m, 3-H) p.p.m.

³ D. H. R. Barton, P. J. L. Daniels, J. F. McGhie, and P. J. Palmer, *J. Chem. Soc.*, 1963, 3675.

⁴ I. G. Guest and B. A. Marples, *J. Chem. Soc. (C)*, 1971, 1468.

$[\phi]_{450} +138^\circ$, $[\phi]_{330} +270^\circ$, $[\phi]_{315} +222^\circ$, $[\phi]_{300} +370^\circ$, and $[\phi]_{270} +920^\circ$, ν_{\max} 1730 (acetate C=O), 1700 (C=O), and 1255 (C=O) cm⁻¹, δ 0.68 (3H, s, 18-H₃), 1.12 (3H, s, 19-H₃), 2.05 (3H, s, 3-OAc), 4.51br (1H, 3-H), and 5.43br (1H, 11-H) p.p.m. (Found: C, 79.6; H, 10.7; O, 10.0. C₃₂H₅₂O₃ requires C, 79.3; H, 10.8; O, 9.9%).

(ii) Elution with light petroleum-benzene (7 : 3; 150 ml) gave a pale yellow solid which crystallised from chloroform-methanol as needles (0.05 g), m.p. and mixed m.p. [with 3β-acetoxylanost-8-en-7-one (5)] 145–149° (lit.,³ 145–148°), δ 0.65 (3H, s, 18-H₃), 1.20 (3H, s, 19-H₃), 2.02 (3H, s, 3-OAc), and 4.48br (1H, 3-H) p.p.m.

(iii) Further elution with light petroleum-benzene (7 : 3; 900 ml) gave a yellow solid (0.9 g) shown by t.l.c. in benzene to be a mixture of compounds (5), R_F 0.11, and (6) R_F 0.15.

(iv) Further elution with light petroleum-benzene gave a yellow solid (0.1 g) which crystallised from chloroform-methanol in yellow plates, m.p. and mixed m.p. [with 3β-acetoxylanost-8-ene-7,11-dione (6)] 154–156° (lit.,⁶ 158–159°), δ 0.79 (3H, s, 18-H₃), 1.17 (3H, s, 32-H₃), 1.30 (3H, s, 19-H₃), 2.01 (3H, s, 3-OAc), and 4.47 (1H, t, J 7 Hz, 3-H) p.p.m.

Isomerisation of 3β-Acetoxy-8-ene-7,11-dione (4).—

⁵ K. Bloch, F. Gautschi, and J. D. Johnston, *J. Biol. Chem.*, 1957, 224, 185.

⁶ L. Ruzicka, E. Rey, and A. C. Muhr, *Helv. Chim. Acta*, 1944, 27, 472.

A solution of the acetoxy-enone (4) (1.5 g, 3.1 mmol) and potassium hydroxide (0.5 g) in methanol (25 ml) was heated under reflux for 2.5 h. It was then poured into water and the precipitate was extracted with ether. Work-up yielded a product which crystallised from ethyl acetate-methanol in needles of 3 β -hydroxylanost-8-en-7-one (5; OH for OAc) (1.2 g, 80%), identified by mixed m.p., i.r., and n.m.r. spectra, and t.l.c.

Oxidation of 3 β -Acetoxy-8 α ,9 α -epoxylanostane (2) and

3 β -Acetoxylanosta-7,9(11)-diene (3) under Marker's Conditions.—Solutions of the epoxide (2)⁴ and the diene (3)⁴ (50 mg, 0.1 mmol) were oxidised similarly. T.l.c. of the products in benzene showed that they contained the three products (4)—(6).

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